

## WHAT IS CLAIMED:

1. A composition comprising at least one purified and isolated autoantigenic fragment wherein said fragment is produced from an autoantigen of a pre-apoptotic cell by the action of at least one lymphocyte granule enzyme, wherein said fragment has at least one terminus derived from the cleavage site of said enzyme.  
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2. The composition of claim 1 wherein the granule enzyme is Granzyme B.  
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3. The composition of claim 2 wherein the autoantigenic fragment is derived from an autoantigen that is a substrate for a caspase and the fragment is produced by the Granzyme B catalyzed cleavage of said protein at a site that is not cleaved by caspase.  
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4. The composition of claim 2 comprising an autoantigenic fragment produced by the Granzyme B catalyzed cleavage of an autoantigen selected from the group consisting of DNA PK<sub>cs</sub>, PARP and NuMA.  
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5. The composition of claim 4 comprising at least one autoantigenic fragment selected from the group consisting of DNA-PK<sub>cs</sub> from amino acid 2699 to 4096; DNA-PK<sub>cs</sub> from amino acid 3211 to 4096; PARP from amino acid 1 to 538; PARP from amino acid 538 to 1004;  
25 NuMA from amino acid 412 to 2111 and NuMA from amino acid 1 to 1799.  
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6. A pharmaceutical composition comprising at least one purified and isolated autoantigenic fragment having at least one terminus derived from a granule enzyme cleavage site, wherein said cleavage site is not cleaved by a caspase, and a pharmaceutically acceptable carrier.  
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7. The composition of claim 6 wherein the granule enzyme is granzyme B.

8. The composition of claim 6 wherein the autoantigenic fragment is selected from the group of fragments consisting of DNA-PK<sub>cs</sub> from amino acids 2699 to 4096; DNA-PK<sub>cs</sub> from amino acids 3211 to 4096; PARP from amino acid 1 to 538; PARP from amino acids 538 to 1004; 5 NuMA from amino acids 412 to 2111 and NuMA from amino acids 1 to 1799.

9. The pharmaceutical composition of claim 6 comprising at least one autoantigenic fragment derived from a malignant cell.

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10. A method of treating a patient in need of treatment for an autoimmune disease comprising administering at least one autoantigenic fragment of claim 1.

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11. The method of claim 10 wherein the treatment is prophylactic.

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12. The method of claim 10 wherein the autoantigenic fragment is selected from the group of fragments consisting of DNA-PK<sub>cs</sub> from amino acids 2699 to 4096; DNA-PK<sub>cs</sub> from amino acids 3211 to 4096; PARP from amino acids 538 to 1004; NuMA from amino acids 412 to 2111 and NuMA from amino acids 1 to 1799.

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13. The method of claim 10 wherein the method is a method of tolerizing said patient to the presence of said fragment comprising the steps of:

- (a) identifying a target tissue and isolating cells from the tissue,
- (b) providing at least one lymphocyte granule enzyme,
- (c) contacting the cells with said at least one lymphocyte granule enzyme to produce at least one autoantigenic fragment,
- (d) administering said at least one autoantigenic fragment to the patient.

14. The method of claim 13 wherein said at least one lymphocyte granule enzyme provided in step (b) is isolated from the contents of a lymphocyte granule.

5 15. The method of claim 10 for the therapeutic treatment of a patient producing autoantigenic fragments and autoantibodies against the fragments comprising the steps of:

(a) providing an isolated autoantigenic fragment associated with the autoimmune condition in the patient,

10 (b) contacting the serum of the patient with the autoantigenic fragment under conditions that allow the binding of autoantibodies to said autoantigenic fragment.

15 16. The method of claim 15 wherein at least a portion of the autoantibodies are removed from the serum of the patient.

17. The method of claim 15 wherein the autoantibodies are bound to the isolated autoantigenic fragment *in vivo*.

20 18. A method of treating a patient in need of treatment for a malignancy comprising the steps of

(a) providing at least one enzyme of a lymphocyte granule,  
(b) isolating malignant cells from the patient,  
(c) contacting the malignant cells with the enzyme to

25 produce a mixture containing autoantigenic fragments, and

(d) administering the autoantigenic fragments to the patient.

30 19. An assay for the detection of an autoantigenic fragment in a patient as an indication of the presence or absence of an autoimmune condition in a patient comprising:

(a) providing a sample from the patient,  
(b) contacting the sample with an antibody that specifically binds to a cryptic epitope of an autoantigenic fragment, said

fragment having at least one terminus derived from a granule enzyme cleavage site,

5 (c) detecting the presence or absence of the binding of the antibody to the autoantigenic fragment as an indication of the presence or absence of an autoimmune condition in a patient.

20. The assay of claim 19 wherein the granule enzyme is granzyme B.

10 21. An assay for the detection of an antibody that binds an autoantigenic fragment as an indication of the presence or absence of an autoimmune condition in a patient comprising:

(a) providing a sample from the patient,  
(b) contacting the sample with an autoantigenic fragment  
15 having at least one terminus derived from cleavage by a granule enzyme,  
(c) detecting the presence or absence of the binding of an antibody in the sample to the autoantigenic fragment as an indication of the presence or absence of an autoimmune condition in the patient.

20 22. The assay of claim 21 wherein the granule enzyme is granzyme B.

25 23. A method of making an autoantigenic fragment from an autoantigen comprising the steps of

(a) isolating cells containing at least one autoantigen, and  
(b) contacting the cells with a lymphocyte granule enzyme  
to produce a mixture containing at least one autoantigenic fragment.

30 24. The method of claim 22 further comprising the step of  
(c) isolating said at least one autoantigenic fragment.

25. The method of claim 22 wherein step (a) further comprises purifying at least one autoantigen from the cells and step (b) comprises contacting said purified autoantigens with granzyme B.

26. The method of claim 25 wherein in step (a) the at least one autoantigen is at least one of DNA-PK<sub>cs</sub>, PARP and NuMA, and step (b) comprises contacting said at least one autoantigen with granzyme B.

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27. The method of claim 22 wherein said lymphocyte granule enzyme is isolated from the granules of at least one lymphocyte selected from the group consisting of cytotoxic T lymphocytes (CTL), natural killer cells (NK), lymphokine activated killer cells (LAK) and cells 10 of the YT cell line.

28. A method of identifying candidate agents for preventing or treating autoimmune disease symptoms comprising:

15 a) contacting a test substance with at least one granule enzyme and an autoantigen which is a substrate for said at least one granzyme enzyme;

b) monitoring the cleavage of the autoantigen said enzyme into autoantigenic fragments;

20 c) determining whether the candidate agent alters the production of the autoantigenic fragments;

wherein a test substance which inhibits the cleavage is identified as a candidate agent for treating autoimmune diseases.

29. The method of claim 28 wherein the granule enzyme is 25 granzyme B.